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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,734	02/26/2002	David Needham	5405-212IPDV	3807

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,734	NEEDHAM, DAVID	
	Examiner	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57,59-64 and 66-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57,59-64 and 66-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 6-21-04 is acknowledged.

Claims included in the prosecution are 57, 59-64 and 66-78.

Claim Rejections - 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 66, 69-71, 73-74 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Ogawa (5,094,854)).

Ogawa discloses liposome compositions various drugs for hyperthermia therapy. The liposomes contain a mixture of lipids including the claimed combination and various drugs. (note the abstract, col. 1, line 58 through col. 4, line 37; Examples and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant based on the results in Example 2 (figure 2) of instant application argue that liposomes that have a bilayer of pure DPPC become unstable near the phase transition temperature, causing release of some of the CF and that Ogawa does not teach the second claimed component. These arguments are not found to be persuasive. Addressing applicant's second point first, the examiner points out that

according to instant claims the second component is a palmitoyl surfactant or myristoyl surfactant or stearoyl surfactant and Ogawa teaches a combination of DPPC and DSPC and according instant claims, the first component is a phosphatidylcholine. Since phospholipids are surfactants, Ogawa teaches the combination of instant first component and second component. Since Ogawa's formulations are for the release of the active component above the physiological temperature that is between 40 and 45 degrees Ogawa meets the requirements of instant claims.

3. Claims 66 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl (5,626,867).

Eibl discloses liposomal formulations containing DPPC and DSPA (second component). The liposomes contain a variety of active agents including anti-tumor agents (note the abstract, col. 1, line 65 through col. 2, line 43, col. 4, line 39 through line 61; Examples, example 1 in particular and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Eibl fails to disclose the second component. According to applicant DSPA taught by Eibl is not a lysolipid. The examiner agrees; however, as pointed out above, according to instant claims, the second component is a stearoyl surfactant and DSPA taught by Eibl is distearoyl phosphatidic acid and phospholipids are surfactants.

4. Claims 66-69 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Alving (4,416,872).

Alving discloses liposomal formulations containing DPPC and a ceramide Second component. The liposomes contain a quinoline active agent. The method of preparation involves hydrating the lipid film with the aqueous medium. (Note abstract, Examples and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the new claims describe liposomes wherein the active agent is rapidly released from the liposomes at 39 to 45 degrees and Alving neither teaches nor suggests a composition having this feature. This argument is not found to be persuasive since instant claims are composition claims and an intended claim limitation has no significance. Alving teaches a liposome composition containing the same composition and therefore, meets the limitations of instant claims. With regard to applicant's arguments that Alving teaches away since he emphasizes the slow effectiveness through slow biodegradation of the multilamellar structure of the liposomes is not persuasive for the same reasoning. Furthermore, instant claims do not exclude this slow degradation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 66, 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hristova (Macromolecules, vol. 28, pp. 7693-7699, 1995) in combination with Ogawa cited above.

Hristova discloses liposomal formulations containing dipalmitoylphosphatidylcholine and a lysolipid. The liposomes further comprise PEG derivatized lipids. Although Hristova does not teach instant lysolipid, monopalmitoylphosphatidylcholine, Hristova discusses the effect if lysolipids in general on gel phase bilayers and provides a specific example of the effect of the lysolipid, monooleoylphosphatidylcholine (note the abstract, Materials and Methods and Discussion). Therefore, it would have been obvious to one of ordinary skill in the art to use any lysophosphatidylcholine (that is substituted with any fatty acid moiety) with the expectation of obtaining similar effect on the gel phase bilayers. Hristova does not teach specific encapsulated active agents or a method of administration using hyperthermia (heating). However, in the introduction part, Hristova clearly suggests that the liposomes are for drug delivery, though not using hyperthermia.

Ogawa as pointed out above, teaches that DPPC has a transition temperature of 41.4 degrees and the use of liposomes containing DPPC for hyperthermia therapy (note the abstract, col. 1, line 58 through col. 4, line 37; Examples and claims).

It would have been obvious to one of ordinary skill in the art to use liposomes containing DPPC of Hristova for the delivery of active agents by hyperthermia therapy with a reasonable expectation of success since Ogawa teaches that DPPC has a transition temperature of 41.4 degrees and liposomes containing this phospholipid could be used successfully for the delivery of active agents using hyperthermia therapy.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the new claims describe liposomes wherein the active agent is released from the liposome at 39 to 45 degrees and that Hristova does not teach or suggest this feature. These arguments are not persuasive since Hristova teaches the same claimed combination of phospholipids and suggestive of drug delivery and therefore, the composition would be expected to behave the same way when subjected to heat and could be used in hyperthermia therapy as also taught by Ogawa.

7. Claims 66, 69-75, and 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alving in combination with Ogawa both cited above.

The teachings of Alving have been discussed above. What are lacking in Alving are the teachings of using hyperthermia to release the active agent.

Ogawa as pointed out above, teaches the principle of release of active agent using temperatures higher than the transition temperatures of the lipids using Hyperthermia.

The use of hyperthermia for the release of active agent in Alving would have been obvious to one of ordinary skill in the art with a reasonable expectation of success Since Ogawa teaches that hyperthermia can be used to release the active agent from the liposomes.

8. Claims 57, 60-64 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogawa, Eibl, Alving, Hristova cited above, further in view of either Boni (5,820,848) or Bracken (5,756,121).

The teachings of Ogawa, Eibl, Hristova and Alving have been discussed above. These references teach the classical method of preparation of liposomes containing the

active agents. What is lacking in these references is the loading of the active agent in gel phase lipids that is below the transition temperature.

Boni while disclosing various methods of preparation of liposomes teaches that the temperature of the liposomes can be below the main transition temperature of the lipid (example 4).

Bracken teaches hydrating the lipid with an amino glycoside at a temperature significantly below the transition temperature of the lipid mixture (col. 4, lines 25-32).

To load the liposomes of Ogawa or Eibl, or Alving with the active agent at the gel phase, that is below the transition temperature would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the references of Boni and Bracken each teach the feasibility of such loading.

9. Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ogawa, Eibl, Alving, Hristova in combination with either Boni or Bracken as set forth above, further in view of Mayer et al (chemistry and Physics of Lipids, vol. 40, 1986).

Ogawa, Eibl and Alving, Hristova, Boni and Bracken do not all teach the loading of drugs by a pH gradient.

Mayer et al disclose that loading of drugs into liposomes using PH gradients is advantageous since one can achieve trapping efficiencies approaching 100 %.

The use of pH gradient loading method for loading the drugs in the liposomes of Ogawa, Eibl or Alving, Hristova, Boni and Bracken would have been obvious to one of ordinary skill in the art since one can achieve higher trapping efficiencies as taught by Mayer et al.

Applicant's arguments have been fully considered, but are found to be moot in view of this new rejection.

Double Patenting

10. Upon consideration, the double patenting rejections of claims over claims in 5,827,533, 5,882,679, 6,143,321 are withdrawn. In view of the terminal disclaimer, the Double patenting rejection over claims in 6,200,598 is withdrawn

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GSK

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615